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The effect of inflammatory scores on the prognosis of malignant mesothelioma

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ABSTRACT

Aims: Malignant mesothelioma (MM) is a rare cancer with a poor prognosis that is frequently detected late in the disease's progression. The purpose of our sudy was to contribute to the literature by investigating how inflammation indices such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), prognostic nutritional index (PNI), systemic inflammation response index (SIRI), and HALP scores affect disease progression and prognosis in patients with MM.

Methods: This study retrospectively examined 85 patients pathologically diagnosed with malignant pleural and peritoneal mesothelioma. NLR, PLR, LMR, PNI, SIRI, and HALP scores of the patients were calculated.

Results: The area under the curve (AUC) values obtained by ROC analysis are NLR (0.65), PLR (0.67), LMR (0.66), PNI (0.64), SIRI (0.66), and HALP (0.77). The cut-off values were as follows: NLR (3.2), PLR (168.5), PNI (35.2), LMR (2.5), SIRI (2.2) and HALP (22.8). In multivariate analysis, being inoperable was found to be associated with lower survival, while receiving chemotherapy and high PNI value were found to be associated with higher survival ($p<0.05$).

Conclusion: In our study, patients with high PNI had longer median survival time. This score can serve as a simple and useful scoring system for predicting the prognosis of malignant pleural mesothelioma in clinical practice.

Keywords: Inflammation indices, malignant mesothelioma, prognostic nutritional index

INTRODUCTION

Malignant mesothelioma (MM) is a cancer that develops in the thin layer of tissue that surrounds organs in the chest or abdomen. Pleural mesothelioma develops in the lining of the lung and accounts for around 75% of cases. People with this kind of cancer have the highest survival rate.[1]

Chronic inflammation is an important factor in determining the prognosis of various types of cancer, including MM. Relationships between survival and inflammation indices have been shown in various types of cancer, including neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), platelet distribution width (PDW)/platelet count ratio (PPR), prognostic nutritional index (PNI), lymphocyte/monocyte ratio (LMR), HALP score and systemic inflammation response index (SIRI), but studies on MM are limited. These parameters can be calculated simply by looking at the laboratory values of patients in daily practice.[2-4]

Systemic inflammatory diseases have emerged as a significant indicator of malignant tumors in recent years and are intimately linked to the development, spread, metastasis, and resistance to medication. Platelets, a crucial component of inflammation, are involved in both the development of cancer and inflammation. In order to promote tumor growth, blood vessel creation, and metastasis, tumor cells have the ability to trigger immune cell migration to tumor sites. Additional physiological roles of albumin as a gauge of the body's nutritional state include preserving plasma osmotic pressure, promoting tissue growth and repair, transferring endogenous and exogenous substances like different medications or nutrients, and controlling systemic inflammation. NLR, LMR and PLR are markers of systemic inflammatory response. There are studies in the literature in which high NLR, low LMR and high PLR predict shorter survival before treatment.[5,6]

The primary cells involved in the body's immunological response are lymphocytes. As a heterogeneous antigen, they can trigger the body to mount an immune response and generate a significant number of lymphocytes during the growth of malignancies. Tumor cells may express antigens that suppress immune cells when immune evasion occurs, which will cause immune cells to adhere to the tumor and undergo death. Patients with hypoalbuminemia are more likely to experience postoperative problems, tumor growth and migration, infection, and inflammation, all of which might

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decrease their prognosis. Since its introduction by Chen et al.[8] in 2015, the HALP score, which takes into account the patient's immunological and nutritional status, has been demonstrated to be an independent predictor of gastric cancer outcome. The prognosis of various cancer types has also been linked to the HALP score in recent years.[7,8]

PNI was first devised to assess perioperative immunonutritional status and surgical risk in patients undergoing gastrointestinal surgery. It is based on the total lymphocyte count in peripheral blood and the serum albumin concentration.[9] Emerging inflammatory markers SIRI, PNI, and HALP are good indicators of the body's nutritional condition and chronic inflammation.

The potential importance of certain inflammation indices in MM has not been thoroughly addressed, despite the fact that inflammation indices and their predictive usefulness have been examined in a variety of cancer types. The purpose of our study was to contribute to the literature by investigating how inflammation indices such as NLR, PLR, LMR, PNI, SIRI, and HALP scores affect disease progression and prognosis in patients with MM.

METHODS

The study included 85 patients over the age of 18 who were pathologically diagnosed with malignant pleural and peritoneal mesothelioma and did not have any secondary malignancy. It was designed as a single-center, cross-sectional, and retrospective study. The study was conducted with the permission of Health Sciences University Dr. Abdurrahman Yurtaslan Ankara Oncology SUAM Non-interventional Clinical Researches Ethics Committee (Date: 17.10.2024, Decision No: 2024-10/142). This research was conducted in conjunction with the Helsinki Declaration (revised in 2013).

NLR, PLR, LMR, PNI, SIRI, and HALP scores were calculated with the following formulas;

NLR: Neutrophil count (/μL)/lymphocyte count (/μL),

PLR: Platelet count (10^9/L)/lymphocyte count (/μL),

LMR: Lymphocyte count (/μL)/monocyte count (/μL),

PNI: 10×Serum albumin (g/dl)+0.005×lymphocyte count (/μL)]

SIRI: NLR×monocyte count (/μL),

HALP: Hemoglobin (g/dl)×serum albumin (g/L)xlymphocyte count (/μL)]/platelet count (/L).

Inclusion Criteria for the Study

- Patients over the age of 18,
- Patients whose demographic information, additional disease information, laboratory values, tomography results, pathology reports and 6-month prognosis information can be accessed from the hospital system or patient files will be included in the study.

Exclusion Criteria for the Study

- Patients whose researched criteria cannot be accessed from the patient file or computer environment,
- Patients with active infection,
- Patients using steroids,
- Patients with secondary malignancies will be excluded from the study.

Statistical Analysis

Descriptive statistics and statistical analyses of the study variables were performed using the SPSS 27.0 package program. In all statistical tests performed at a 95% confidence interval, a p value of <0.05 was considered statistically significant. ROC analysis was applied to determine the optimum NLR, PLR, PNI, LMR, SIRI and HALP cut-off values with high sensitivity and specificity. Patients were classified according to these values. Survival among categorized groups was evaluated using Log-rank curves and Kaplan-Meier tests. Multivariate analysis was performed on statistically significant data using Cox regression analysis. Analysis results were presented as median (25%-75% quartile range), mean, standard deviation and hazard ratio (HR). Clinically significant p<0.200 data were also included in the multivariate analysis.

RESULTS

A total of 85 patients were included in the study. 70.6% of the patients had pleural and 29.4% had peritoneal mesothelioma. The median age of the patients was 68 (59.50-76.50). 56.5% of the patients were male, 51.8% had asbestos exposure, and 32.9% were smokers. 43.5% of the patients were inoperable, while 31 patients (36.5%) had an ECOG value ≥2. The clinicopathological characteristics of the patients are shown in **Table 1**. The cut-off values were as follows: NLR (3.2), PLR (168.5), PNI (35.2), LMR (2.5), SIRI (2.2) and HALP (22.8). Parameters were grouped as low and high according to the cut-off values. While no significant difference was found in terms of survival time in NLR, PLR, LMR, HALP and SIRI values, high PNI value were found to be associated with higher survival (p<0.05).

Univariate and multivariate analyses were evaluated by Cox regression analysis. In multivariate analysis, being inoperable was found to be associated with lower survival, while receiving chemotherapy were found to be associated with higher survival (p<0.05). The results of univariate and multivariate analyses for survival are shown in **Table 2**.

The median survival time of operable patients was 14 months, while the median survival time of inoperable patients was 8 months. The difference was found to be statistically significant (p<0.05). The median survival time of patients who received chemotherapy was 12 months, while the median survival time of patients who did not receive chemotherapy was 4 months, and the difference was found to be statistically significant (p<0.05). Finally, the median survival time of patients with high PNI was 14 months, while the median survival time of

Table 1. Clinicopathological features and inflammatory markers of patients

	Median (25-75 CI)	
Age (year)	68.00 (59.50-76.50)	
Survival time (months)	12 (12-26)	
	Category	n (%)
Gender	Male	48 (56.5)
	Female	37 (43.5)
Tumor localization	Pleura	60 (70.6)
	Peritoneum	25 (29.4)
Asbestos exposure	Yes	44 (51.8)
	No	41 (48.2)
Smoke	Non smoker	57 (67.1)
	Smoker	28 (32.9)
Operation status	Operable	48 (56.5)
	Inoperable	37 (43.5)
ECOG PS	0-1	54 (63.5)
	≥2	31 (36.5)
Chemotherapy	Yes	76 (89.4)
	No	9 (10.6)
Radiotherapy	Yes	27 (31.8)
	No	58 (68.3)
Pathological diagnosis	Epitheloid	72 (84.7)
	Sarcomatoid	6 (7.1)
	Biphasic	7 (8.2)
NLR	≤3.2	34 (40.0)
	>3.2	51 (60.0)
PLR	≤168.5	34 (40.0)
	>168.5	51 (60.0)
LMR	≤2.5	48 (56.5)
	>2.5	36 (42.4)
PNI	≤35.2	56 (65.9)
	>35.2	29 (34.1)
SIRI	≤2.2	35 (41.2)
	>2.2	50 (58.8)
HALP	≤22.8	53 (62.4)
	>22.8	32 (37.6)

CI: Confidence interval, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, LMR: Lymphocyte/monocyte ratio, PNI: Prognostic nutritional index, SIRI: Systemic inflammation response index, HALP: Hemoglobin*albumin*lymphocyte/platelet ratio

patients with low PNI was 10 months, and the difference was found to be statistically significant (p<0.05).

DISCUSSION

This study evaluated the prognostic significance of certain inflammation indices in MM including PNI, NLR, PLR, LMR, HALP and SIRI which which have previously been examined in other types of cancer. Several studies have previously been undertaken to evaluate prognostic variables in MM. Each study looked at different prognostic variables. The quest for a predictive biomarker has switched to inflammatory markers, owing to the long-standing concept that inflammation plays a role in the development of MM.[10] It has been postulated that inflammation may be a contributing factor to MM, and so inflammatory indicators may have a role in disease prognosis. Several studies have found that high PLR and NLR are poor prognostic variables in MM patients.[11,12]

Males often have a higher incidence of malignant pleural mesothelioma than females.[13] Due to relatively recent use restrictions and a 40-year lag between exposure and presentation, incidence is still rising in many countries. The usage of asbestos in developing nations is still on the rise.[14] Men are more likely than women to have the condition, and numerous studies have shown that women have higher survival rates than men. In our study, the median age of the patients was 68. 56.5% of the patients were male, 51.8% had asbestos exposure. The median age is 68, and when the literature was examined, it was seen to be higher compared to other studies conducted in Turkey.[15]

NLR was not identified as a prognostic factor at the time of MM diagnosis in a study by Tural et al.[16] or in a retrospective analysis of 274 patients. Disease queries with low NLR and PLR scores were not statistically significant, according to a different study examining the predictive significance of PLR scores in MM patients.[17] However, in our investigation, we found no significant association between NLR or PLR and OS. Perhaps our limited sample size and the varied NLR-PLR cut-off values are the cause of this insignificance.

Malnutrition contributes significantly to shorter OS, lower quality of life, and higher mortality from malignant cancers. Serum albumin levels are the most extensively used serological indicators of malnutrition. Several studies have found that blood albumin, a simple and objective measure of nutritional status, is an independent predictive factor for malignant pleural mesothelioma.[18] The prognostic role of PNI in MM was investigated in the study conducted by Zhou-Hong et al.[19] While the median OS and one-year survival rate in patients with PNI <44.6 were 18 months and 72.3%, these rates were 11 months and 45.5% in patients with PNI ≥44.6. Ebinç et al.[20] discovered that a high PNI value is a good prognostic factor for MM, but Mutlu et al.[2] found no significant association between high PNI value and OS. In our study, the median survival time for patients with high PNI was 14 months, whereas the median survival time for patients with low PNI was 10 months, and the difference was shown to be statistically significant (p<0,05). There were no research in the literature that examined the association between MM prognosis and HALP, SIRI, and LMR. However, in our investigation, there was no statistically significant relationship between these inflammatory indicators and the prognosis of MM. In our analyses, being inoperable was associated with lower survival, while receiving chemotherapy and a high PNI value were associated with higher survival.

MM is a rare malignant tumor with strong invasiveness and poor prognosis. In a study conducted in our nation with 55 MM patients, the median OS was 13 months. It climbed to 16 months in the pleural MM subgroup, but declined to 9 months in the peritoneal MM group.[2] The median OS in Dogan et al.'s[21] study of patients with pleural and peritoneal MM was 22 months, whereas in a large series of 910 patients analyzing just patients with pleural MM, the median OS was 10 months. However, the effect of induction chemotherapy and adjuvant high-dose hemithoracic radiation on outcome following extrapleural pneumonectomy for MPM is still debated, and further research is needed to identify the patient population most likely to benefit from this aggressive strategy. In our analysis, 43.5% of the patients were inoperable, with 31 (36.5%) having an ECOG score of ≥2. While 89.4% of the patients got platinum-based chemotherapy, 27 (31.8%)

Table 2. Results of univariate and multivariate analysis for survival

	Category	Median survival time (months)	Single analysis HR 95% CI	P	Multiple analysis HR 95% CI	p
Age	<65*	14				
	>65	12	1.20 (0.72-1.98)	0.471		
Gender	Male*	12				
	Female	12	1.32 (0.81-2.15)	0.262		
Tumor localization	Pleura*	12				
	Peritoneum	12	1.29 (0.76-2.19)	0.344		
Operation status	Operable*	14				
	Inoperable	8	1.82 (1.10-2.45)	**0.018**	1.94 (1.14-3.31)	**0.014**
ECOG PS	0-1*	12				
	>2	12	1.01 (0.62-1.66)	0.954		
Chemotherapy	Yes*	4				
	No	12	0.58 (0.27-1.22)	0.152	0.45 (0.21-0.98)	**0.047**
Radiotherapy	Yes*	10				
	No	18	0.87 (0.53-1.45)	0.610		
Pathological diagnosis	Epitheloid *	12				
	Sarcomatoid	2	1.80 (0.77-4.21)	0.174	2.07 (0.86-4.98)	0.101
	Biphasic	6	1.37 (0.54-3.45)	0.501	1.41 (0.54-3.70)	0.475
NLR	≤3.2*	12				
	>3.2	12	1.33 (0.79-2.24)	0.272		
PLR	≤168.5*	12				
	>168.5	12	1.37 (0.81-2.31)	0.228		
LMR	≤2.5*	12				
	>2.5	12	0.86 (0.52-1.44)	0.582		
PNI	≤35.2*	10				
	>35.2	14	0.37 (0.20-0.69)	**0.002**	0.35 (0.17-0.74)	**0.006**
SIRI	≤2.2*	12				
	>2.2	12	1.12 (0.67-1.87)	0.646		
HALP	≤22.8*	12				
	>22.8	12	0.61 (0.36-1.06)	0.084	0.95 (0.50-1.79)	0.880

*Reference category, HR: Hazard ratio, CI: Confidence interval, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, LMR: Lymphocyte/monocyte ratio, PNI: Prognostic nutritional index, SIRI: Systemic inflammation response index, HALP: Hemoglobin*albumin*lymphocyte/platelet ratio

required adjuvant radiotherapy. The better survival time of patients who received treatment was an expected result and was consistent with the literature.

Limitations

This study has some limitations. It was retrospective, and a prospective multicenter study would be much better in terms of evaluating the prognostic factors of MM. The study's reduced patient count and missing data may lead to bias in some conclusions.

CONCLUSION

In our study, patients with high PNI had longer median survival time. This score can serve as a simple and useful scoring system for predicting the prognosis of malignant pleural mesothelioma in clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of Health Sciences University Dr. Abdurrahman Yurtaslan Ankara Oncology SUAM Non-interventional Clinical Researches Ethics Committee (Date: 17.10.2024, Decision No: 2024-10/142).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
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Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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